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09/857,000	09/07/2001	Philippe Clair	19904-012 NAT	7846

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EXAMINER	
KAM, CHIH MIN	
ART UNIT	**PAPER NUMBER**
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/857,000	CLAIR ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *2,3 and 5-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4 and 9-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 January 2007* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/4/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-11 are pending.

Applicants' amendments filed December 4, 2006 and January 4, 2007 are acknowledged. Applicants' response has been fully considered. Claims 1 and 4 have been amended, and new claims 9-11 have been added. Claims 2-3 and 5-8 are non-elected inventions and withdrawn from consideration. Therefore, claims 1-4 and 9-11 are examined.

Oath/Declaration

2. A new oath or declaration filed December 4, 2006 is defective because non-initialed and/or non-dated alterations have been made to the addresses of inventors, Philippe Clair and Jamal Temsamani. However, in some cases, a deficiency in the oath or declaration can be corrected by a supplemental paper such as an application data sheet (see 37 CFR 1.76 and MPEP 601.05).

Withdrawn Informalities

3. The previous objection to the specification regarding Figs. 1, 2, 6, 11, 12 and 15, is withdrawn in view of applicant's submission of replacement sheets of Figs. 1, 2, 6, 11, 12 and 15 in the amendment filed January 4, 2007.

Withdrawn Claim Objections

4. The previous objection to claims 1 and 4 is withdrawn in view of applicant's amendment to the claim in the amendment filed December 4, 2006.

Informalities

The disclosure is objected to because of the following informalities:

5. Applicants have added "SEQ ID NO:5" for SynB3 cited in table VIII at page 31, line 4, and "SEQ ID NO:6" for SynB1 cited in Table IX at page 33, line 4 in the amendment filed January 4, 2007. However, the amino acid sequence of SynB1 is not SEQ ID NO:6 and the amino acid sequence of SynB3 is not SEQ ID NO:5 in the Sequence Listing. The specification also recites amino acid sequences in Tables I and VII without providing "SEQ ID NO:" . Appropriate correction is required.

Claim Objections

6. Claims 9-11 are objected to because the claim recites peptides of SynB1 and SynB3 without providing the sequence identifier "SEQ ID NO:".

Maintained Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 1 and 4 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Response to Arguments

Applicants indicate new claims 9-11 are directed to methods for diagnosis of a Central Nervous System (CNS) disease, for treatment of a Central Nervous System (CNS) disease, and for driving a substance across the Blood Brain Barrier (BBB) to the Central Nervous System (CNS), respectively. Furthermore, applicants submit an Information Disclosure Statement containing several articles to provide the Examiner a better understanding of the subject matter

recited in new claims 9-11, Applicant submits articles pertaining to the use of linear peptides to enable the transport of various active molecules across the Blood Brain Barrier (BBB) (pages 7-10 of the response).

Applicants' response has been considered, however, the arguments are not persuasive because claims 1 and 4 recite "a use" without providing any steps involved in the process, results in an improper definition of a process under 35 U.S.C. 101. The new claims 9-11 recite the method steps in a process and are not rejected under 35 U.S.C. 101.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1 and 4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a method of preparing a conjugate of an active substance and a linear peptide of formula (II), which is capable to pass through the hemato-encephalic barrier to reach brain, by covalently coupling the linear peptide with the active substance, wherein the active substance is a chemical molecule (i.e., doxorubicin or penicillin) or a peptide (i.e., dalargine), and wherein the linear peptide is SynB1 (RGGRLSYSRRRFSTSTGR, SEQ ID NO:11), does not reasonably provide enablement for a method of preparing a medicine of a linear peptide of formula (II), its retro form, or a fragment of at least 5 successive amino acids coupled to an active substance, which is capable to pass through the hemato-encephalic barrier to be used for diagnosis or therapy of a disorder localized in the CNS, wherein the sequence of the linear peptide, the active substance and the disorders are not defined. The specification does not

enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1 and 4 encompass a method of preparing a medicine of a linear peptide of formula (II) coupled to an active substance, which is capable to pass through the hemato-encephalic barrier to be used for diagnosis or therapy of a disorder localized in the CNS. The specification, however, only discloses cursory conclusions (page 3, line 22-page 4, line 27) without data supporting the findings, which state that a linear peptide derived from an antibiotic peptide having the formula (I), (II) or (III), or moieties of the peptides, can be used to vector one or more active substances to pass through the hemato-encephalic barrier for therapeutic and diagnostic applications. There are no indicia that the present application enables the full scope in view of the use of the linear peptides of formula (II) in vectoring the active substance as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the linear peptides of formula (II), their retro forms or fragments of at least 5 amino acids; the active

substance; and the disorders to be diagnosed or treated, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification demonstrates penetration of doxorubicin into brain using doxo-SynB1 and doxo-SMP-3MP-SEQ ID NO:13 (Example 1); penetration of dalargine into brain using dal-SynB1 (Example 2); penetration of doxorubicin into brain using doxo-SynB3 (Example 3); and penetration of penicillin into brain using PNC-SynB1 (PNC, benzylpenicillin; Example 4). The only linear peptide in the formula (II) tested as a vector for transporting is SynB1, and there are no working examples indicating the vectoring effects of various peptides contained in formula (II), their retro forms or fragments, and the treatment of various disorders localized in CNS using these conjugates. Please note that SynB3 is not a compound of formula (II).

(3). The state of the prior art and relative skill of those in the art:

The related art has shown the structures of antibiotic peptides such as protegrin and tachyplesin that have disulfide bonds (e.g., references cited at page 4 of the specification). However, the general knowledge and level of the skill in the art do not supplement the omitted description such as identification of various linear peptides of formula (II), their retro forma or fragments that can vector an active substance to pass through the hemato-encephalic barrier to reach brain, thus the specification needs to provide this guidance for enabling for all variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to a method of preparing a medicine of a linear peptide of formula (II) coupled to an active substance, which is capable to pass through the hemato-

encephalic barrier to be used for diagnosis or therapy of a disorder localized in the CNS. While the specification demonstrates SynB1 or SynB3 as a vector for transporting doxorubicin, dalargine or penicillin into brain (Examples 1-4), there are no working examples indicating the vectoring effects of various peptides contained in formula (II), their retro forms or fragments, and the treatment of various disorders localized in CNS using these conjugates. Furthermore, the specification fails to identify any other linear peptides of formula (II) that have vectoring effect. Moreover, the specification does not provide any specific guidance on the identification of fragments or retro forms of linear peptides of formula (II). Since the specification does not provide sufficient teachings on the identities of active linear peptides of formula (II), it is necessary to carry out undue experimentation to identify the active peptides from formula (II).

(5). Predictability or unpredictability of the art:

As indicated in the previous sections, there is only one linear peptide of formula (II) (SynB1; SynB3 is not a compound of formula (II)) identified as a vector for transporting some specific active substance into brain. Because the amino acid sequences of formula (II) are highly variable, it is not known whether all the peptides of formula (II) would have the same vectoring effect as SynB1, and it is not readily apparent that one would have been able to a`priori predict the vectoring effect of each peptide of formula (II).

(6). Nature of the Invention

The scope of the claims includes many structural variants, but the specification has not shown how to identify the active peptides from numerous peptide variants or fragments. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods associated with the variants, the teachings in the specification are limited, the sequences of active peptides are unpredictable, therefore, it is necessary to have additional guidance and to carry out undue experimentation to identify the active peptides that can transport active substances to pass through the hemato-encephalic barrier into brain.

Response to Arguments

Applicants indicate new claims 9-11 are directed to methods for diagnosis of a Central Nervous System (CNS) disease, for treatment of a Central Nervous System (CNS) disease, and for driving a substance across the Blood Brain Barrier (BBB) to the Central Nervous System (CNS), respectively. Applicants request the Examiner refer to the articles submitted in the Information Disclosure Statement and the comments set forth above (page 10 of the response).

Applicants' response has been considered, however, the arguments are not persuasive because of the following reasons. As indicated in paragraph 8 (see above), claims 1 and 4 encompass many structural variants of compounds of formula (II), but the specification has not provided sufficient information regarding identification of active peptides from numerous variants or fragments of compounds of formula (II), thus it requires undue experimentation to identify the active peptides from compounds of formula (II). The references in the IDS merely provide the linear peptides of SynB1 and SynB3 can vector small molecules or peptides across the Blood Brain Barrier (BBB), they do not provide sufficient information regarding identification of active peptides from compounds of formula (II) or the use of compounds of formula (II) in the treatment or diagnosis of CNS diseases. Thus, the rejection is maintained.

9. Claims 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of vectoring an active substance across the blood brain barrier (BBB) to the central nervous system (CNS) by preparing a conjugate of SynB1 or SynB3 covalently coupling with an active substance, and administering the conjugate to a patient, wherein the active substance is a chemical molecule (i.e., doxorubicin or penicillin) or a peptide (i.e., dalargine), does not reasonably provide enablement for a method of diagnosis or treatment of a CNS disease, or a method of driving a substance across the BBB to the CNS using the conjugate of SynB1 or SynB3 covalently coupling with an active substance, wherein the active substance and the diseases are not defined. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 9-11 encompass a method of diagnosis or treatment of a CNS disease, or a method of driving a substance across the BBB to the CNS using the conjugate of SynB1 or SynB3 covalently coupling with an active substance. The specification, however, only discloses cursory conclusions (page 3, line 22-page 4, line 27) without data supporting the findings, which state that a linear peptide derived from an antibiotic peptide having the formula (I), (II) or (III), or moieties of the peptides, can be used to vector one or more active substances to pass through the hemato-encephalic barrier for therapeutic and diagnostic applications. There are no indicia that the present application enables the full scope in view of the use of the conjugate of SynB1 or SynB3 in treating or diagnosing a CNS disease, or vectoring an active substance as discussed in the stated rejection. The present application does not provide sufficient teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether

undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence or absence of working examples, the state of the prior art and relative skill of those in the art, the predictability or unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the active substances and the diseases to be diagnosed or treated, which are not adequately described or demonstrated in the specification.

(2). The absence or presence of working examples:

The specification demonstrates penetration of doxorubicin into brain using doxo-SynB1 and doxo-SMP-3MP-SEQ ID NO:13 (Example 1); penetration of dalargine into brain using dal-SynB1 (Example 2); penetration of doxorubicin into brain using doxo-SynB3 (Example 3); and penetration of penicillin into brain using PNC-SynB1 (PNC, benzylpenicillin; Example 4). There are no working examples indicating using the conjugates in the treatment or diagnosis of various disorders localized in CNS.

(3). The state of the prior art and relative skill of those in the art:

The related art has shown the structures of antibiotic peptides such as protegrin and tachyplesin that have disulfide bonds (e.g., references cited at page 4 of the specification). However, the general knowledge and level of the skill in the art do not supplement the omitted description regarding using the conjugates of SynB1 or SynB3 covalently coupling with an active substance in the treatment or diagnosis of various disorders localized in CNS.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claimed invention is directed to a method of diagnosis or treatment of a CNS disease, or a method of driving a substance across the BBB to the CNS using the conjugate of SynB1 or SynB3 covalently coupling with an active substance. While the specification demonstrates SynB1 or SynB3 as a vector for transporting doxorubicin, dalargine or penicillin into brain (Examples 1-4), there are no working examples indicating the treatment or diagnosis of various disorders localized in CNS using the conjugates. Furthermore, the specification does not provide any specific guidance on the use of the conjugate in the treatment or diagnosis of various CNS diseases. Since the specification does not provide sufficient teachings on the use of conjugates of SynB1 or SynB3 covalently coupling with an active substance in the treatment, it is necessary to carry out undue experimentation to assess the effects of the conjugates in the treatment or diagnosis of various CNS diseases.

(5). Predictability or unpredictability of the art:

The claimed invention is directed to a method of diagnosis or treatment of a CNS disease, or a method of driving a substance across the BBB to the CNS using the conjugate of SynB1 or SynB3 covalently coupling with an active substance. While the specification indicates SynB1 or SynB3 can transport some specific chemical molecules or peptides into brain, the specification does not provide sufficient information in the use of the conjugates in the treatment or diagnosis of various CNS diseases, it is not known whether the conjugates can treat or diagnose various CNS diseases effectively.

(6). Nature of the Invention

The scope of the claims encompass the use of conjugates in treating or diagnosing various CNS diseases, but the specification does not provide sufficient information in the use of the conjugates in the treatment or diagnosis of various CNS diseases. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed methods, the teachings in the specification are limited, the effects of the conjugates are unpredictable, therefore, it is necessary to carry out undue experimentation in the use of conjugates in the treatment or diagnosis of various CNS diseases.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1 and 4 provide for the use of a linear peptide coupled to an active substance to vector the active substance passing through the hemato-encephalic barrier for diagnosis or therapy of a disorder localized in the CNS, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

11. Claims 1 and 4 are indefinite because of the use of the term "may be". The term "may be" renders the claim indefinite, it is unclear whether groups b or groups X is identical or different. Claim 4 is included in the rejection because it is dependent on a rejected claim and does not correct the deficiency of the claim from which it depends.

12. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation "composed of a sequence of at least 5", and the claim also recites "preferably at least 7 successive amino acids of peptides" which is the narrower statement of the range/limitation.

13. Claim 4 is indefinite because of the use of the terms "Aib" and "Abu". The terms "Aib" and "Abu" render the claim indefinite, it is unclear what the term means. A full name should be indicated at the first occurrence.

Response to Arguments

Applicants indicate new claims 9-11 are directed to methods for diagnosis of a Central Nervous System (CNS) disease, for treatment of a Central Nervous System (CNS) disease, and for driving a substance across the Blood Brain Barrier (BBB) to the Central Nervous System (CNS), respectively. Applicants request the Examiner refer to the articles submitted in the Information Disclosure Statement and the comments set forth above (page 10 of the response).

Applicants' response has been considered, however, the arguments are not persuasive because the rejection is not directed to claim 9-11, but to claims 1 and 4. Since applicants do not respond to the rejection, the rejection is maintained.

14. Claims 9-11 are indefinite because the claim lacks essential steps in the process. The missing steps are effective amount of the conjugate administered, and the outcome of the treatment, it is not clear how the CNS disease is diagnosed using the conjugate, and what is the endpoint of the treatment in the claimed methods.

Conclusions

15. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Bragdon can be reached at 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chih-Min Kam, Ph. D.
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PRIMARY EXAMINER

CMK
March 22, 2007